REMARKS

Applicant respectfully requests reconsideration of this application in view of the foregoing amendments and the following remarks.

A. Status of the Claims

Upon entry of the foregoing amendments, claims 1-22 will remain pending in the application. No claims presently are being amended, added or canceled.

B. The Withdrawal of Claims 13-22 Is Improper

At page 2 of the Office Action, the Examiner indicated that claims 13-22 are pending in the application, but "withdrawn from consideration as being drawn to subject matter which would require a new search and different considerations for patentability." This is improper.

Even if claims 13-22 require "a new search and different considerations," that is not a legitimate basis for withdrawing them from consideration. Applicants added claims 13-22 into the application after a non-final Office Action. At that juncture, the Examiner lacks the authority and the discretion to ignore new claims simply because they present a need for further search and consideration. Significantly, the Examiner did not allege that claims 13-22 are directed to a separately patentable invention from claims already under review. For at least these reasons, Applicants urge the Examiner to give claims 13-22 full consideration.

C. Claims 1-10 and 12 Are Patentable over the Cited Art

Claims 1-10 and 12 were rejected under 35 U.S.C. § 103 as allegedly being obvious over U.S. patent No. 4,919,937 ("Mauvais-Jarvis") in view of Atkinson *et al.*, *Cancer Epidemiology, Biomarkers & Prevention*, 8: 863-866 (1999) ("Atkinson") as evidenced by Boyd *et al.*, *JNCI*, 87: 670-675 (1995) ("Boyd") and Kolb *et al.*, *Radiology*, 225: 165-175 (2002) ("Kolb"). Mauvais-Jarvis allegedly teaches a method of treating breast conditions by percutaneously administering an aqueous alcoholic gel comprising trans-4-hydroxy tamoxifen. The breast conditions are said to include "benign cancerous affections." Atkinson allegedly teaches that tamoxifen reduces mammographic breast density. Combining these two references, the rejection alleges that it would have been obvious to administer 4-hydroxy

tamoxifen percutaneously (as taught by Mauvais-Jarvis) for reducing breast density (as Atkinson taught that tamoxifen does). Applicant traverses the rejection.

The rejection fails to identify any reason for expecting that 4-hydroxy tamoxifen would have the same effect on mammographic breast density as tamoxifen. The two are separate compounds with distinct biological properties and effects.

As explained at paragraphs 22-23 of the specification, although 4-hydroxy tamoxifen is a tamoxifen metabolite, its usefulness for reducing breast density is not presaged by previous experience with tamoxifen itself. Tamoxifen is extensively metabolized by cytochrome P-450 in humans. Thus, its action *in vivo* is the net result of individual actions by the parent compound and its metabolite compounds competing for the occupation of receptors within target tissues. See, for example, Jordan *et al.*, *Breast Cancer Research and Treatment*, 2: 123-138 (1982) (already of record). Each of these compounds manifests different and unpredictable biological activities in different cells, determined in part by each compound's individual effect on estrogen receptor conformation. That is, estrogen receptor binding of each compound generates a unique receptor-ligand conformation that recruits different cofactors, and results in varying pharmacologies for the different compounds. See, for example, Wijayaratne *et al.*, *Endocrinology*, 140(12): 5828-5840 (1999), and Giambiagi *et al.*, *J. Steroid Biochem.*, 30(1-6): 213-217 (1988), both already of record.

Several examples of these varying effects have been documented. For instance, tamoxifen but not 4-hydroxy tamoxifen is a potent rat liver carcinogen. See Carthew *et al.*, *Archives of Toxicology*, 75: 375-380 (2001), and Sauvez *et al.*, *Carcinogenesis*, 20(5): 843-850 (1999), both already of record. Additionally, tamoxifen but not 4-hydroxy tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells. See Dietze *et al.*, *J. Biological Chemistry*, 276(7): 5384-5394 (2001) (already of record). By contrast, 4-hydroxy tamoxifen exhibits a significant inhibitory effect on estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little or no effect in this regard. See Chetrite *et al.*, *Anticancer Research*, 13: 931-934 (1993), already of record.

Applicants acknowledge that 4-hydroxy tamoxifen and tamoxifen are related compounds with similarities. However, even if those similarities made it obvious to try substituting 4-hydroxy tamoxifen for tamoxifen in reducing breast density (which they did not), "obvious to try" is an incorrect standard for evaluating obviousness. *Hybritech, Inc. v. Monoclonal antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 107 s. Ct. 1606 (1987). Moreover, the known biological non-equivalence of the two compounds, as discussed above, demonstrates that those skilled in the art would have no reasonable expectation of success using 4-hydroxy tamoxifen in place of tamoxifen.

As Mauvais-Jarvis, Atkinson and the other cited art fails to teach or suggest the claimed invention's success, Applicant respectfully requests withdrawal of the obviousness rejection.

D. Claim 12 Is Patentable over the Cited Art

Claim 11 was rejected under 35 U.S.C. § 103 as allegedly being obvious over Mauvais-Jarvis and Atkinson as evidenced by Boyd and Kolb in view of Tan *et al.*, *AAPS PharmSciTech*, 1, Article 24, (2000) ("Tan"), and Alberti *et al., J. Controlled Release*, 71: 319-327 (2001) ("Alberti"). Tan allegedly teaches the use of hydrophilic polymers, including Carbopol and hydroxypropyl cellulose, to improve bioadhesive properties. Alberti allegedly teaches the topical delivery of terbinafine using a vehicle consisting of ethanol and isopropyl myristate. Applicant traverses the rejection.

Neither Tan nor Alberti compensates for the deficiencies of Mauvais-Jarvis, Atkinson and the other art, as explained above. Accordingly, Applicant respectfully requests withdrawal of the obviousness rejection.

E. Concluding Remarks

Applicant believes that this application is in condition for allowance, and respectfully requests favorable reconsideration of it.

If the Examiner believes that an interview would advance prosecution of the application, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extension of time is needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 5/24/06

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